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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,003	ZANETTI, MAURIZIO	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *9,10,24,25,36,37 and 45-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-23,26-35 and 38-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment received on 6/9/05 has been entered. Applicant's response to the election/restriction requirement received on 2/16/05 has previously been entered. Claims 1-50 are pending in the instant application. Applicant's election without traverse of the subject matter of Group I, and further species (c), one or more epitopes contained within the CDR of an immunoglobulin molecule" in the reply filed on 2/16/05 is acknowledged. Claims 9-10, 24-25, 36-37, and 45-50 are therefore withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2/16/05. Claims 1-8, 11-23, 26-35, and 38-44 are currently under examination in the instant application. An action on the merits follows.

Nucleotide and/or Amino Acid Sequences

This application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Specifically, the specification contain numerous sequence disclosures, both nucleotide and amino acid, that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a)(1) and (a)(2) and which are not identified by SEQ ID NO. Please note that compliance to 37 CFR 1.821-1.825 requires that the specification be amended to recite SEQ

ID NOS. for each recitation of a sequence in the specification. Further, it is unclear whether these sequences are present in the paper copy and CRF of the sequence listing filed in this application. If the sequences are present in the paper and CRF listings, applicant may fully comply with 37 CFR 1.821 by amending the specification to include the proper SEQ ID NOS. If the sequences are not present on the filed paper and CRF listings, then new paper and CRF sequence listings are required as set forth in the Notice to Comply.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, 11-23, 26-35, and 38-44 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38-44 of copending Application No. 09/300,959, hereafter referred to as the '959 application. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claims 38-44 of the '959 application represent a species of claims 1-8, 11-23, and 26-31 of the instant invention. Independent claim 1 of the instant invention is broadly drawn to methods for stimulating an immune response by administering ex vivo to a lymphoid cell a nucleic acid molecule comprising a hematopoietic cell-specific expression element operationally linked to a nucleic acid encoding one or more heterologous epitopes, and independent claim 17 is drawn to methods for stimulating an immune response by administering to a lymphoid cell a nucleic acid molecule comprising a hematopoietic cell-specific expression element operationally linked to a nucleic acid encoding one or more heterologous epitopes. Independent claims 38-41 of the '959 application also recite methods for stimulating an immune response but are narrower in that they are limited to the administration of a plasmid vector encoding a B cell expression element operationally linked to a nucleic acid sequence encoding one or more heterologous epitopes, and are further limited to the administration of the plasmid vector ex vivo to B cells. It is well established that a species of a claimed invention renders the genus obvious. *In re Schaumann* , 572 F.2d 312, 197 USPQ 5 (CCPA 1978). In regards to the particular limitations of instant dependent claims 2-8, 11-16, 18-23, and 26-35, note that these limitations are clearly taught in the specification of the '959 application and are encompassed by the '959 claims. For example, see the '959 specification at pages 23-25. Thus, as a species of the instant invention, claims 38-43 of the '959 application render instant claims 1-8, 11-23, and 26-31 obvious.

In regards to instant claims 32-35, and 38-44, claim 44 of the '959 application is both broader and narrower in scope than the instant claims. Claim 44 of the '959 application is narrower than the instant claims in that it is limited to a plasmid vector comprising a B cell expression element, whereas the instant claims broadly read on any nucleic acid molecule

comprising a hematopoietic cell-specific expression element. However, the instant claims are narrower in that they are further limited to wherein the nucleic acid encodes two or more T cell epitopes (claim 32), or wherein the two or more T cell epitopes are inserted within a CDR of an immunoglobulin molecule (claim 38). Claim 44 of the '959 application encompasses these embodiments as it recites that the plasmid encodes one or more heterologous epitopes. Further, the specification of the '959 application clearly teaches these embodiments, see for instance pages 29-30. Thus, claim 44 of the '959 application is both a species of the instant invention and further encompasses the narrower limitations regarding T cell epitopes recited in the instant claims. As such, instant claims 32-35, and 38-44 are rendered obvious by claim 44 of the '959 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 11-23, 26-35, and 38-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA plasmid comprising an immunoglobulin heavy chain enhancer/promoter operatively linked to an immunoglobulin molecule containing one or more heterologous antigenic epitopes inserted within one or more

CDR of the immunoglobulin molecule, and methods of stimulating an immune response *in vivo* by intrasplenic injection of a plasmid DNA comprising an immunoglobulin heavy chain enhancer/promoter operatively linked to an immunoglobulin molecule containing one or more heterologous antigenic epitopes inserted within one or more CDR of the immunoglobulin molecule, does not reasonably provide enablement for any nucleic acid comprising a hematopoietic cell-specific expression element operatively linked to an immunoglobulin molecule containing one or more heterologous antigenic epitopes inserted within one or more CDR of the immunoglobulin molecule or the use of such nucleic acids to generate immune responses by administering the nucleic acids to any lymphoid tissue or cell *in vivo* or *ex vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification is broadly drawn to the use of nucleic acid molecules encoding heterologous epitopes operatively linked to hematopoietic cell-specific expression elements to generate immune responses in mammal capable of treating a condition or disease, specifically viral and other pathogenic infections. The claims read broadly on the use of any expression element capable of directing specific expression of a gene in any hematopoietic cell, and the use of any type of nucleic acid, i.e. linear nucleic acids, plasmid vectors, viral vectors etc., comprising the expression elements and the heterologous epitopes. The specification further broadly discloses that the nucleic acids can be delivered to any type of lymphoid tissue or lymphoid cell either directly *in vivo* or *ex vivo* in tissue culture, wherein the lymphoid cells contacted *ex vivo* are then returned to the mammal, such that an immune response is generated.

The specification fails to provide sufficient guidance for identifying and using hematopoietic cell-specific expression elements other than the immunoglobulin heavy chain enhancer/promoter in the nucleic acids of the instant invention. The specification, while broadly disclosing "hematopoietic cell-specific expression elements" fails to provide any guidance for any expression element other than the immunoglobulin heavy chain enhancer/promoter, whose activity is limited to B cells. The specification does not disclose any expression elements capable of directing expression of a heterologous gene or epitope in any other type of hematopoietic cell or lymphoid cell such as T cells, macrophages, dendritic cells, hematopoietic stem cells, eosinophils, basophils, granulocytes, or NK cells. Further, the specification does not provide any guidance to structures or functions shared between the immunoglobulin heavy chain enhancer/promoter and other hematopoietic cell specific expression elements, such that the skilled artisan would be able to identify or isolate other expression elements useful in the instant nucleic acids. Further, while the art at the time of filing teaches that many different types of expression elements were known, a high degree of unpredictability existed regarding the ability of different expression elements to effectively direct the expression of a gene sequence in the context of different expression vector systems and in different cell types. Verma et al., cites an example of an *ex vivo* gene expression attempt where a retrovirus was used to express factor IX in fibroblasts which were then grafted into an immunocompromised murine host. According to Verma, " within five to seven days of transplanting the infected cells back into mice, expression of factor IX is shut off", and that appropriate enhancer-promoter combinations are necessary to override the 'off switch'. Verma concludes by stating that, "the search for such combinations is a case of trail and error for a given cell type" (Verma, (1997) Nature, Vol. 389, 239-242, see

page 240). Bohm et al. further teaches that, " the relevant antigen-presenting cell (APC) that primes class I-restricted CTL and/or class II-restricted helper T cells specific for [an immunogen] after DNA immunization is unknown" and that, "many promoter sequences display cell type-specific variability in gene expression" (Bohm et al. (1996) J. Immunol. Methods, Vol. 193, page 30, column 2, lines 28-32, and 35-37). In particular, Bohm et al. demonstrated that of seven vector constructs encoding a viral immunogen tested in mice, only five were capable of generating an immune response, and that of those five, only three which utilized the strong CMV promoter efficiently generated both an antigen specific antibody and CTL response (Bohm et al. *supra*, page 32, Figure 1, and page 38, column 1, paragraph 2, and column 2). Therefore, in view of the art recognized unpredictability in determining whether a particular promoter will be capable of effectively expressing a gene sequence in a particular cell in the context of particular vector, the lack of guidance in the specification for any hematopoietic cell-specific expression element other than the immunoglobulin heavy chain enhancer/promoter, and the breadth of the claims, it would have required undue experimentation to make and use the nucleic acids as claimed comprising any hematopoietic cell-specific expression element.

Furthermore, in regards to the use of different vector systems to express gene sequences of interest in cells *in vivo*, the art at the time of filing teaches that achieving therapeutic levels of gene expression using currently available vector systems, including retroviruses, adenoviruses, or plasmid DNA, was considered highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. supra, page 239, column 3, paragraph 2). Marshall concurs, stating that, " difficulties in getting genes transferred

efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, 1050-1055, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", 1-23, page 1, paragraph 3, and page 8, paragraph 2). The specification, while broadly teaching the use of any nucleic acid to express the heterologous epitopes, only provides specific guidance for the use of plasmid DNA. In particular, the working examples are limited to the intrasplenic injection of a plasmid vector comprising the immunoglobulin heavy chain enhancer/promoter operatively linked to an immunoglobulin heavy chain comprising a heterologous viral epitope inserted into a CDR. The specification fails to provide sufficient guidance for utilizing other vector systems such that lymphoid cells are transfected/transduced and sufficient levels of the encoded epitope(s) are expressed which are capable of inducing T and/or B cell immune responses. Thus, in view of the art recognized unpredictability in using different vector systems to express therapeutically effective amounts of an encoded gene in a desired cell type, the breadth of the claims, and the lack of specific guidance in the specification for using vector systems other than plasmid DNA vectors, it would have required undue experimentation to practice the scope of the invention as claimed.

The instant claims, see claims 17-23, and 26-31, further read on targeting specific lymphoid tissue or lymphoid cell types *in vivo*. While the specification contemplates the direct injection of nucleic acids into particular lymphoid tissue, i.e. lymph nodes, Peyer's patches etc., the claims are not so limited. The claims read on targeting a lymphoid tissue using any route of administration, or targeting any particular lymphoid cell type using any route of administration. However, the specification does not provide sufficient guidance for selecting vectors and routes of administration capable of delivering the claimed nucleic acids to specific tissues or cell types other than direct intrasplenic injection of plasmid DNA. At the time of filing, the skilled artisan did not consider the targeting of vectors to specific cell types *in vivo* to be predictable . Deonarain, in a review entitled, " Ligand-targeted receptor-mediated vectors for gene delivery", teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al. (1998) Exp. Opin. Ther. Patents, Vol. 8 (1), page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al. (1995) FASEB, Vol. 9, page 198, paragraph 2). In addition, the art recognized that the site of administration of the nucleic acid and physiological conditions at the site, and further the natural tropism of nucleic acids which are viral vectors, determines which cell types can be exposed and transfected/transduced. For instance, intravenous injection of nucleic acid, and adenoviral

vectors in particular, results primarily in the accumulation of the nucleic acid in the liver, not in lymphoid tissue. Therefore, in view of the art recognized unpredictability in targeting particular cells and tissues using current vector systems, the natural tropism of viral vectors, the effects of the site of administration, the lack of guidance provided by the specification for using routes of administration other than intrasplenic injection to target lymphoid tissue, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

Finally, claims 1-8, and 11-16 read broadly on contacting any lymphoid cell *ex vivo* with the claimed nucleic acids in order to stimulate a B and/or T cell response. The specification teaches that lymphoid cell types can be removed from a mammal, transfected/transduced *ex vivo/in vitro*, and reintroduced into a mammal in order to induce an antigen specific immune response. Lymphoid cell types encompass numerous types of cells including B cells, T cells, macrophages, dendritic cells, follicular dendritic cells, NK cells, and stromal cells. However, as noted above, at the time of filing, the skilled artisan did not know which type of antigen presenting cell or combination of antigen presenting cell types are necessary and sufficient to prime or stimulate T cells and B cells to expressed heterologous antigens (see Bohm et al., *supra*). While the specification speculates that B cells are transfected following intrasplenic injection of plasmid DNA and are thus responsible for the resulting observed immune responses in the working examples, the specification does not demonstrate that B cells by themselves, or any other type of lymphoid cell by itself is capable of stimulating T and or B cell responses to expressed antigen following injection by any route to any site in a mammal. The working examples demonstrate that syngeneic splenic lymphocytes, a mixed population of spleen cells,

transfected with plasmid DNA comprising the immunoglobulin heavy chain enhancer/promoter operatively linked to an immunoglobulin heavy chain comprising a heterologous viral epitope inserted into a CDR, are capable of generating antigen specific immune responses *in vivo* following intravenous injection. While the immunoglobulin promoter would limit the expression of the epitope to B cells, it is unclear whether the B cell themselves are responsible for the observed responses, or whether antigen shed from the B cell is picked up by other types of cell in the splenocyte population which then stimulate immune responses, or whether it is a combination of the two. In addition, while splenocytes contain large numbers of B cells, other lymphoid organs do not. If B cells are responsible for the observed immune stimulation, then it is unclear whether a population of lymphoid cell derived from urogenital tissue or lymph nodes, which contains significantly less B cells than spleen, would be capable of stimulating effective immune responses against encoded antigen. Thus, based on the number of different cell types found in lymphoid tissue, the differing composition of cell types between different lymphoid tissues, the unpredictability in the art concerning which types of antigen presenting cells are responsible for stimulating T and B cells responses, the limitation of the working examples to transfected splenocytes, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to practice the breadth of the claims as written.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 11-16, and 38-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8 and 11-16 are incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 1, upon which claims 2-8 and 11-16 depend, recite a method for stimulating an immune response comprising administering *ex vivo* to a lymphoid cell a nucleic acid. Since the net result of following the steps in the claim as written appears to be cells contacted with a nucleic acid *in vitro*, it is unclear how an immune response can be stimulated since immune stimulation requires the presence of the epitope in a subject. The following method steps appear to be lacking: a step wherein the lymphoid cells are transfected with the nucleic acid; a step wherein the transfected cells are administered to a subject mammal; and a step wherein the expression of the heterologous epitope(s) in the lymphoid cell results in the stimulation of an immune response in the subject mammal.

Claims 38-44 are indefinite in that they lack antecedent basis for "said heterologous peptide". The claim is drawn to a nucleic acid molecule comprising a nucleic acid sequence encoding one or more "heterologous epitopes". Claims 39-44 depend on claim 38 and thus are included in this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32-33, 35, 38-39, 41-42, and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Xiong et al. (1997) Nat. Biotech., Vol. 15, 882-886. The applicant claims a nucleic acid molecule comprising a hematopoietic cell-specific expression element operatively linked to a nucleic acid sequence encoding two or more T cell epitopes wherein said nucleic acid sequence encodes an immunoglobulin molecule containing said epitopes inserted within more than one CDR of the immunoglobulin molecule. The applicant further claims said nucleic acids wherein the immunoglobulin comprises a heavy chain variable region, wherein the T cell epitopes are a CD4 epitope and a CD8 epitope, and wherein the expression element function in a B cell.

Xiong et al. teaches plasmid vectors comprising an immunoglobulin heavy chain enhancer/promoter operatively linked to a heavy chain immunoglobulin sequence comprising a variable region wherein two heterologous epitopes are inserted into the CDR2 and CDR3 regions of the immunoglobulin molecule (Xiong et al., pages 883, Figure 1, and 885). Xiong et al. further teaches wherein the two epitopes inserted into the CDR2 can be a T helper epitope (i.e. a CD4 epitope) and a B cell epitope, or a T helper epitope and a CTL epitope (i.e. a CD8 epitope) (Xiong et al., page 885, column 1, paragraph 2). Thus, by teaching all the elements of the claims as written, Xiong et al. anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 11-23, 26-35, and 38-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xiong et al. (1997) Nat. Biotech., Vol. 15, 882-886, in view of US 5,969,109 (10/19/99), hereafter referred to as Bona et al., and US 2002/0007173 A1 (1/17/02), hereafter referred to as Kundig et al. The applicant claims a nucleic acid molecule comprising a hematopoietic cell-specific expression element operatively linked to a nucleic acid sequence encoding two or more T cell epitopes wherein said nucleic acid sequence encodes an immunoglobulin molecule containing said epitopes inserted within more than one CDR of the immunoglobulin molecule. The applicant further claims said nucleic acids wherein the immunoglobulin comprises a heavy chain or light chain variable region, wherein the T cell epitopes are a CD4 epitope and a CD8 epitope, two CD4 epitopes, or two CD8 epitopes, or a

combination of two T cell epitopes and a B cell epitope, and herein the expression element function in a B cell. The applicant further claims methods of stimulating an immune response by administering said vectors to lymphoid cells either *ex vivo* or *in vivo*, wherein the lymphoid cells are derived from or present in lymph nodes, blood, tonsils, Peyer's patches, MALT and NALT.

Xiong et al. teaches plasmid vectors comprising an immunoglobulin heavy chain enhancer/promoter operatively linked to a heavy chain immunoglobulin sequence comprising a variable region wherein two heterologous epitopes are inserted into the CDR2 and CDR3 regions of the immunoglobulin molecule (Xiong et al., pages 883, Figure 1, and 885). Xiong et al. further teaches wherein the two epitopes inserted into the CDR2 can be a T helper epitope (i.e. a CD4 epitope) and a B cell epitope, or a T helper epitope and a CTL epitope (i.e. a CD8 epitope) (Xiong et al., page 885, column 1, paragraph 2). Xiong et al. further teaches administering the vectors by intrasplenic injection to a mammal to stimulate T and B immune responses (Xiong et al., page 883-884).

Xiong et al. differs from the instant invention by not specifically teaching the inclusion of more than two heterologous epitopes in the immunoglobulin molecule. Specifically, Xiong et al. does not teach the inclusion of three epitopes comprising a CD4, a CD8, and B cell epitope in the immunoglobulin. Xiong et al. further does not teach that the immunoglobulin comprises a light chain. However, Xiong et al. does provide motivation for expressing multiple heterologous antigenic peptides in the CDRs of immunoglobulin by teachings that, ".. the possibility of eliciting an immune response in vivo using antigenized H-chain genes allows one to test multiple antigen peptides in various combinations to optimize immunogenicity", and that " [t]he ability to manipulate Ig V region genes and express multiple heterologous peptides in the CDRs opens

new possibilities in the designing of molecules of complex, predetermined antigen specificity and/or complementary immunogenic function .. for vaccination purposes" (Xiong et al., page 885, column 1, paragraph 2). Bona et al. further supplements Xiong et al. by providing detailed direction for making nucleic acids encoding immunoglobulin containing one, two, or more than two different epitopes contained with different CDRs of either the heavy or light chain variable regions of an immunoglobulin molecule (Bona et al., columns 4, 11-12, and 18). In addition, Bona et al. teaches that all three of the CDRs in a variable region can be modified to include a heterologous epitope (Bona et al., column 18). Bona et al. also teaches various B cell epitopes, T helper epitopes, and CTL epitopes which can be included in the immunoglobulin CDRs (Bona et al., columns 9-10). Thus, based on the detailed teachings of Bona et al. for making nucleic acids encoding an immunoglobulin in which more than two heterologous epitopes are inserted into CDRs of either the heavy or light chain variable region of the immunoglobulin gene, and the motivation to express multiple antigenic peptides in immunoglobulin molecules provided by Xiong et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to modify the plasmids taught by Xiong et al. include a third epitope, such as B cell epitope or T cell epitope in order to optimize immunogenicity. Further, based on the high level of skill in the art of modifying CDRs to include heterologous epitopes as evidenced by both Xiong et al. and Bona et al., the skilled artisan would have had a reasonable expectation of success in modifying the plasmids of Xiong to include an additional epitope in CDR1.

Xiong et al. and Bona et al. further differ from the instant invention by failing to teach the administration of nucleic acids encoding chimeric immunoglobulin to lymphoid cells of the blood or lymph nodes *ex vivo* or *in vivo* in order to stimulate immune responses. Kundig et al.,

however, supplements Xiong et al. by providing specific motivation for delivering nucleic acids encoding antigens directly to the lymphatic system, including lymph nodes, Peyer's patches, and tonsils, instead of to the spleen. Kundig et al. teaches the stimulation of immune responses, and specifically T cell responses, by administering vector encoding an antigen or mammalian cells expressing an antigen directly to the lymphatic system (Kundig et al., page 3, column 2). In particular, Kundig et al. teaches delivering vectors such as plasmids or viral vectors, or delivering dendritic cells comprising a recombinant nucleic acid encoding an antigen directly to the lymphatic system to induce a T cell response (Kundig et al., column 34-35, claims 11, 14, 18-19, and 22-23). Kundig et al. provides motivation for directly administering antigen to the lymphatic system by comparing the immune response generated after immunization with nucleic acid encoding an antigen using various routes of immunization including intrasplenic and intranodal injection and demonstrating that intranodal injection generates greater antigen specific T cell responses than intrasplenic injection (Kundig et al, pages 27, and 32-33). Therefore, in view of the motivation provided by Kundig et al. that intranodal injection is superior to intrasplenic injection, it would have been *prima facie* obvious to the skilled artisan to administer the nucleic acids encoding antigenic epitopes taught by Xiong et al. directly to the lymph node instead of the spleen. Further, since Kundig et al. teaches that cells such as dendritic cells comprising nucleic acids can be used in lieu of nucleic acids alone for lymphatic immunization, it would have been *prima facie* obvious to the skilled artisan to administer the nucleic acids taught by Xiong et al. either alone or comprised in dendritic cells in order to stimulate immune responses. Further, in view of the successful use of the nucleic acids taught by Xiong et al. to induce immune responses by intrasplenic injection, and the teachings of Kundig et al. that

intranodal injection increases immune responses to antigen compared to intrasplenic injection, the skilled artisan would have had a reasonable expectation of success in stimulating immune responses by administering a nucleic acid encoding an immunoglobulin comprising two or more heterologous antigenic epitopes inserted in the CDRs of the immunoglobulin to the lymph nodes alone or contained within a dendritic cell.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

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